Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Oral Powder: 40 mg per 1 g of oral powder (one level scoop, measured with supplied dosing scoop = 1 g oral powder)

Tablets: 150 mg, 200 mg, 250 mg, and 300 mg

Fixed-Dose Combination Tablets

- [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Truvada tablet] Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Truvada low-strength tablet]
  - Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg
  - Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg
  - Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate and Infant Dose:

- Tenofovir disoproxil fumarate (TDF) has not been approved by the Food and Drug Administration or recommended for use in neonates and infants aged <2 years.

Child (Aged ≥2 Years to <12 Years) Dose:[a]

- TDF 8 mg/kg per dose once daily

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density[a]

Special Instructions

- TDF oral powder formulation is available for patients who are unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: one level scoop = 1 g powder = TDF 40 mg.
- Mix TDF oral powder with 2 to 4 oz. of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with

TDF Oral Powder Dosing Table

Body Weight	TDF Oral Powder Once-Daily Scoops of Powder
10 kg to <12 kg	2 scoops (80 mg)
12 kg to <14 kg	2.5 scoops (100 mg)
14 kg to <17 kg	3 scoops (120 mg)
17 kg to <19 kg	3.5 scoops (140 mg)
19 kg to <22 kg	4 scoops (160 mg)
22 kg to <24 kg	4.5 scoops (180 mg)
24 kg to <27 kg	5 scoops (200 mg)
27 kg to <29 kg	5.5 scoops (220 mg)
29 kg to <32 kg	6 scoops (240 mg)
32 kg to <34 kg	6.5 scoops (260 mg)
34 kg to <35 kg	7 scoops (280 mg)
≥35 kg	7.5 scoops (300 mg)

TDF Tablet Dosing Table for Patients Aged ≥2 Years and Weighing ≥17 kg

Body Weight	TDF Tablet Once Daily
17 kg to <22 kg	150 mg
22 kg to <28 kg	200 mg
28 kg to <35 kg	250 mg
≥35 kg	300 mg

Child and Adolescent (Weighing ≥35 kg)[a] and Adult Dose:

- TDF 300 mg once daily

[Atripla and Generic] Efavirenz/Emtricitabine/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach.

[Cimduo] Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose:

- One tablet once daily

[Complera] Emtricitabine/Rilpivirine/TDF

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- One tablet once daily in antiretroviral therapy (ART)-naive adults with baseline HIV RNA ≤100,000 copies/mL. This dose of Complera can also be used in virologically suppressed (HIV RNA <50 copies/mL) adults who are currently on their first or second regimen and who have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.

liquid. The powder may float on the top even after vigorous stirring.

- Although TDF can be administered without regard to food, food requirements vary depending on the other ARV drugs contained in an FDC tablet. Food requirements are listed with dosing recommendations and in Table 2 of the Drug Appendix.
- Measure serum creatinine and perform a urine dipstick test for protein and glucose before starting a TDF-containing regimen. Serum creatinine should be monitored and urine should be tested for protein and glucose at intervals during continued therapy (see Table 15i). Measure serum phosphate if there is clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before using TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TDF.
- Tenofovir alafenamide (TAF) is associated with less bone and renal toxicity than TDF, but it has equal antiviral efficacy. **Do not use TAF and TDF together.** Consider switching from TDF to TAF in appropriate clinical settings.

Metabolism/Elimination

TDF Dosing in Patients with Renal Insufficiency:

- TDF is renally excreted.
- The dose of TDF should be decreased in patients with impaired renal function (creatinine clearance [CrCl] <50 mL/min). Consult the manufacturer's prescribing information for directions on how to adjust the dose in accordance with CrCl.
- The FDCs Atripla, Complera, and Symfi Lo should not be used in patients with CrCl <50 mL/min or in patients who require dialysis.
- The FDC Truvada should not be used in patients with CrCl <30 mL/min or in patients who require dialysis.
- The FDC Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

- Administer with a meal of ≥500 calories.

[Delstrigo] Doravirine/Emtricitabine/TDF

Adult Dose:

- One tablet once daily in ART-naive adults. This dose of Delstrigo can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Delstrigo.
- Not studied in children or adolescents (see the Doravirine section for more information)

[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF

Adolescent (Weighing >35 kg with a Sexual Maturity Rating [SMR] of 4 or 5) and Adult Dose:

- One tablet once daily in ART-naive adults. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.
- Administer with food.

[Symfi] Efavirenz 600 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach.

[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach.
- Symfi Lo has not been studied in children (SMR 1 to 3), and major inter-individual variability in efavirenz (EFV) plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs of 1 to 3 who weigh ≥40 kg. Therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients weighing ≥40 kg. See the Efavirenz section for more

information.

[Temixys] Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose:

- One tablet once daily

[Truvada] Emtricitabine/TDF (FTC/TDF)

Child, Adolescent, and Adult Dose:

Truvada Dosing Table

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	One FTC 100 mg/TDF 150 mg tablet
22 kg to <28 kg	One FTC 200 mg/TDF 133 mg tablet
28 kg to <35 kg	One FTC 167 mg/TDF 250 mg tablet
≥35 kg and adults	One FTC 200 mg/TDF 300 mg tablet

[a] See text for a discussion of the concerns about decreased bone mineral density in patients who are receiving TDF, especially in prepubertal patients and those in early puberty (SMR 1 or 2).

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- Tenofovir disoproxil fumarate (TDF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein and breast cancer resistance protein. When TDF is coadministered with inhibitors of these transporters, an increase in TDF absorption may be observed, with the potential for enhanced TDF toxicity.[1]
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of plasma tenofovir (TFV). Avoid frequent or long-term use of nonsteroidal anti-inflammatory drugs in patients who are taking TDF.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine (ddI) serum concentrations increase when this drug is coadministered with TDF, and this combination **should not be used** because of the increased risk of ddI toxicity.
- *Protease inhibitors:* Atazanavir (ATV) without ritonavir **should not be coadministered** with TDF because TDF decreases ATV plasma concentrations. In addition, the combination of ATV and lopinavir/ritonavir increases plasma TFV concentrations and increases the risk of TDF-associated toxicity.[2]
- *Use of Stribild:* If using Stribild, please see the Elvitegravir section of the Drug Appendix for additional information.

Major Toxicities

- *More common:* Nausea, diarrhea, vomiting, flatulence.
- *Less common (more severe):* TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF. Renal toxicity, including increased serum creatinine, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreased serum phosphate, has been observed. Patients at increased risk of renal glomerular or tubular dysfunction should be closely monitored. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

TDF has been approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years when used as a component of antiretroviral therapy (ART). TDF is available as a component of FDC tablets (see Appendix A, Table 2).

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is approved by the FDA for HBV treatment in children aged ≥12 years. The use of TDF to treat HBV/HIV coinfection is reviewed in the Pediatric Opportunistic Infection Guidelines.

Efficacy in Clinical Trials in Adults Compared to Children and Adolescents

The standard adult dose that was approved by the FDA for adults and children aged ≥12 years and weighing ≥35 kg is TDF 300 mg once daily. For children aged 2 to 12 years, the FDA-approved dose is TDF 8 mg/kg per dose administered once daily, which closely approximates the dose of TDF 208 mg/m^2 per dose used in early studies in children.[3]

In adults, the recommended once-daily dose of TDF 300 mg is highly effective. In comparative clinical trials in adults, TDF administered with lamivudine (3TC) or emtricitabine (FTC) as a dual-NRTI backbone in combination with efavirenz (EFV) had better viral efficacy than zidovudine (ZDV) or stavudine (d4T) administered with 3TC and EFV.[4-6] TDF administered with FTC has been compared to abacavir (ABC) administered with 3TC in several adult studies and meta-analyses, with variable results.[7-11]

The FDA approved Cimduo and Temixys (both of which contain 3TC 300 mg/TDF 300 mg) and Symfi (EFV 600 mg/3TC 300 mg/TDF 300 mg) after reviewing the results of a clinical trial that compared the use of TDF to the use of d4T when each drug was administered with 3TC and EFV.[5,12] This trial showed that TDF and d4T had similar virologic response; however, TDF had lower toxicity than d4T.

FDA approval of Symfi Lo (EFV 400 mg/3TC 300 mg/TDF 300 mg) was based on a study that compared the use of EFV 400 mg to the use of EFV 600 mg, each administered with FTC 200 mg and TDF 300 mg, in 630 ART-naive adults.[13] See the Efavirenz section for a detailed discussion of this study.

In children, the published efficacy data for TDF are mixed, but potency equal to that in adults has been seen in pediatric patients aged 3 to 18 years with susceptible virus. In children aged 2 years to <12 years, TDF 8 mg/kg per dose once daily was noninferior to twice-daily ZDV-containing ART or d4T-containing ART over 48 weeks of randomized treatment.[14,15] Virologic success is lower in treatment-experienced patients with extensive drug resistance.[16-18]

Pharmacokinetics

Relationship of Drug Exposure to Virologic Response

Virologic suppression is most closely related to intracellular tenofovir diphosphate (TFV-DP) concentrations, and for TDF, intracellular TFV-DP is linked to plasma TFV concentration.[19] A modeling study suggests that children and adolescents who are treated with TDF may have higher intracellular TFV-DP concentrations than adults,[20] even though plasma TFV concentrations are lower in children and adolescents, because renal clearance of TFV is higher in children than in adults.[3,21,22]

Formulations

Special Considerations

The taste-masked granules that make up the TDF oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed with a vehicle, TDF should be administered promptly because its taste becomes bitter when it is allowed to sit for too long.

Toxicity

Bone Toxicity

TDF administration is associated with decreased BMD in both adults[23,24] and children.[15,25-27] When treated with TDF, younger children with sexual maturity ratings (SMRs) of 1 and 2 may be at a higher risk of decreased BMD than children with more advanced pubertal development (i.e., SMRs ≥3).[21] Discontinuation of TDF results in partial or complete recovery of BMD.[25,28]

In the industry-sponsored study that led to FDA approval of TDF in adolescents aged ≥12 years and weighing ≥35 kg, six of 33 participants (18%) in the TDF arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks, while only one of 33 participants (3%) in the placebo arm experienced this decline.[16]

TDF administration disrupts vitamin D metabolism,[29,30] and the decrease in BMD associated with TDF initiation was attenuated in adults with coadministration of high doses of vitamin D3 (4,000 International Units [IU] daily) and calcium carbonate (1,000 mg daily) for the first 48 weeks of TDF treatment.[31] During chronic TDF administration, youth with HIV who received vitamin D3 supplements (50,000 IU once monthly) had decreased serum parathyroid hormone levels and increased lumbar spine BMD compared to study participants who were not treated with high doses of vitamin D3.[29,32] The serum 25-hydroxy vitamin D concentration was 37 ng/mL in the group with improved BMD. Similar improvements in BMD were seen in youth with HIV who were treated with an antiretroviral (ARV) regimen that included TDF and who received vitamin D3 2,000 IU or 4,000 IU daily.[33] Since this improvement in lumbar spine BMD was seen in patients with and without baseline vitamin D deficiency, some practitioners recommend vitamin D supplementation for all patients who are being treated with an ARV regimen that includes TDF.

High concentrations of the TDF metabolite plasma TFV have been associated with TDF-related endocrine disruption and low BMD.[34] Tenofovir alafenamide (TAF), which is associated with lower plasma TFV concentrations than TDF, has less effect on parathyroid hormone levels[35] and causes less decline in BMD than TDF (see the Tenofovir Alafenamide section for more information). Consider switching from TDF to TAF in patients for whom loss of BMD is of concern.

Monitoring Potential Bone Toxicity

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend routine dual-energy absorptiometry (DXA) monitoring for children or adolescents who are being treated with TDF. Given the potential for BMD loss in children treated with TDF, some experts perform a DXA before initiating TDF therapy and approximately 6 months after starting TDF, especially in prepubertal patients and those who are in the early stages of puberty (i.e., SMRs 1 and 2). If DXA results are abnormal, consider referring the patient to a subspecialist in pediatric endocrinology or a related field.

TDF has been shown to be effective, and it can be administered once daily; however, the use of TDF has been associated with a risk of BMD loss. Because childhood and early adolescence are important periods of rapid bone accrual, and because children with perinatally acquired HIV are at risk for low peak bone mass, the Panel favors the use of ABC or TAF over TDF in children with SMRs 1 to 3.[36,37]

Renal Toxicity

New onset renal impairment and worsening renal impairment have been reported in adults[38] and children[39,40] receiving TDF. In one study, renal toxicity led to discontinuation of TDF in six of 159 (3.7%) of children

with HIV who were treated with TDF.[18] While TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.[38,39] Irreversible renal failure is quite rare, but cases have been reported.[41]

The main target of TDF nephrotoxicity is the renal proximal tubule.[39] Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.[42,43]

Subclinical renal tubular damage is more common than clinically apparent renal tubular injury. Increased urinary beta-2 microglobulin was identified in 12 of 44 children (27%) who were treated with TDF and in two of 48 children (4%) who were not treated with TDF.[44] The risks of TDF-associated proteinuria and chronic kidney disease increase with the duration of treatment.[45,46] Of 89 participants aged 2 to 12 years who received TDF in Gilead Study 352 (where participants had a median drug exposure of 104 weeks), four participants were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.[14]

Plasma TFV is the TDF metabolite most closely associated with both glomerular[34,47] and proximal tubular[48] toxicity. TAF, which generates lower plasma TFV concentrations than TDF, is associated with a lower risk of renal toxicity than TDF (see the Tenofovir Alafenamide section).[49]

Monitoring Potential Renal Toxicity

Because TDF has the potential to decrease creatinine clearance and cause renal tubular dysfunction, the Panel recommends measuring serum creatinine and using a urine dipstick to check protein and glucose concentration before initiating TDF. It is unclear how often creatinine and renal tubular function (urine protein and glucose) should be monitored in asymptomatic patients. Many Panel members monitor creatinine with other blood tests every 3 to 4 months and perform urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and in the absence of proteinuria. Because nephrotoxicity increases with the duration of TDF treatment, monitoring should be continued during long-term therapy with the drug.

Because renal glomerular damage primarily increases the concentration of albumin in urine, and proximal renal tubular damage increases the concentration of low-molecular-weight proteins like beta-2 microglobulin in urine, dipstick urinalysis (which primarily measures urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measuring urine albumin and urine protein and calculating the ratio of urine albumin to urine protein can be helpful in identifying the nonalbumin proteinuria that is seen in TDF-associated nephrotoxicity.[50,51] While these more complex and expensive tests may be used in research settings, in clinical practice, using a renal dipstick to identify normoglycemic glycosuria and proteinuria is the easiest way to detect renal damage.

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